pharmaceutically acceptable salt to a patient in need thereof, wherein the patient does not exhibit lower urinary tract obstruction.

Please insert the following new claims:

---5. (NEW) A method of treating neurogenic bladder comprising administering an effective amount of tamsulosin or a pharmaceutically acceptable salt thereof to a patient with neurogenic bladder.

6. (NEW) A method of treating voiding dysfunction associated with neurogenic bladder, comprising administering an effective amount of tamsulosin or a pharmaceutically acceptable salt thereof to a patient, wherein said voiding dysfunction is not associated with benign prostatic hypertrophy.---

REMARKS

In the Office Action mailed December 9, 2002, the Office considered claim 4. By the present Amendment, claim 4 is amended and new claims 5 and 6 are added. Thus, claims 4-6 are pending upon entry of this Amendment. The support for these amendments is found throughout the specification, and specifically, for example, in the background section that distinguishes the different causes of voiding dysfunction (paragraph bridging pages 1 and 2), and the first paragraph of the Disclosure, which makes clear that the invention is directed to treating voiding dysfunction associated with neurogenic bladder (page 4, last full paragraph).

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Claim Rejections - 35 U.S.C. § 103

The Office rejects claim 4 under 35 U.S.C. § 103(a) as being unpatentable over Yasuda et al. (*The Journal of Urology*, Vol. 156, p. 1125-1130, 1996) in view of U.S. Patent No. 6,071,882, to Engel et al. The Office states that "Yasuda et al. discloses that alpha blockers are effective at improving urinary flow rates and residual urine in cases of voiding dysfunction *caused by benign prostatic hyperplasia (BPH)*," (emphasis added) and that Engel et al. teaches that tamsulosin is an alpha blocker. (Office Action, page 2.) The Office asserts that it would have been obvious to use tamsulosin "to improve urinary flow rates and residual urine in cases of voiding dysfunction caused by BPH, because Yasuda et al. teach that alpha blockers are successful for this very purpose." (Id., pages 2 and 3.) Applicants traverse the rejection.

Initially, Applicant notes that claim 4 is directed to the therapy of voiding dysfunction associated with *neurogenic bladder*, not with BPH. Applicants raised this issue in the previous response, yet the Office has ignored the point. Applicants respectfully submit that the claimed use is a *new* use, and distinct from previous uses of tamsulosin. Yet the Office continues to treat the claim as if it is directed to treating voiding dysfunction generically, regardless of the cause. The Office has ignored the limitation in Applicant's claim that requires that the voiding dysfunction be associated with neurogenic bladder. The Office is ignoring Applicants' inventive new use. Applicant respectfully submits that when the Office considers this element of the claim, the rejection should be withdrawn.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

In the Response to Arguments section, the Office states that "[i]t is not necessary that the prior art be aware of the mechanism which causes the ailment to be treated . . . [I]t is only necessary that the prior art teach the treatment of the particular ailment." To exemplify the point, the Office asserts that Advil (ibuprofen) and Tylenol (acetaminophen) are "known to treat headaches, whether the headaches are caused by blunt force trauma to the head, dehydration, or sinus congestion." (Office Action, page 3.)

With respect, Applicant submits that the underlying mechanisms of disease are important in determining a treatment, and it is not as simple as suggesting that all headaches can be effectively treated with ibuprofen or acetaminophen. Often, different diseases manifest the same symptoms. It would be imprudent, indeed, contrary to established medical principles, to treat a symptom without considering the underlying cause.

The observed symptom, such as voiding dysfunction or headache, can *be* the disease (primary), or be a symptomatic manifestation of an underlying disease (secondary). To use the Office's example, *Harrison's Principles of Internal Medicine, 15th Edition* (Chapter 15 of which is attached and listed on a Form PTO-1449, and is hereinafter referred to as *Harrison*), lists headaches that are primary diseases, such as migraine, Tension-type headache, Cluster headache, etc., and secondary diseases, such as headaches associated with brain tumor, subarachnoid hemorrhage, meningitis, giant cell arteritis, etc. (See Table 15-1 on page 71.) "Headache is usually a benign symptom, but occasionally it is the manifestation of a serious illness such as brain

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

tumor, subarachnoid hemorrhage, meningitis, or giant cell arteritis. . . . [I]t is imperitive that the serious causes of headache be diagnosed rapidly and accurately." (*Harrison*, page 70, introductory paragraph.) Clearly, those skilled in the art would not simply advise administration of acetaminophen or ibuprofen in response to *any* headache complaint. In situations in which the headache is secondary to a serious underlying malady, while analgesics might be given to palliate, treatment of the malady may be critical to relieving the headache.

Even in cases in which the headache is the primary disease, the choice of treatment is not invariable and should take into account the underlying cause. For example, classic migraine headaches, which can be very severe, are believed to result from changes in cranial blood flow and neurogenic inflammation. (*The Merck Manual*, Sec. 14, Ch. 168, Headache, page 1 of 2, first full paragraph of "Etiology and Pathophysiology." A copy of the section is attached and hereinafter referred to as *The Merck Manual*.) These headaches do not respond well to over-the-counter headache medicines, such as acetaminophen, aspirin, and ibuprofen. (*The Merck Manual*, page 2 of 2, last full paragraph under "Treatment.")

While it is not entirely understood what causes classic migraines, the serotonin receptor has been implicated. Understanding this etiology has led to the preferred method of treatment, which involves the use of serotonin (5-hydroxytryptamine $[5HT]_{1B/1D}$) receptor agonists, generically referred to as triptans. The triptans have a number of effects that are attributed to their interaction with serotonin receptor subtypes, including suppression of neurogenic inflammatory changes, inhibition of

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
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central nausea and vomiting, and vasoconstriction of meningeal blood vessels. ("Drug Interactions and The Triptans," *CNS News Special Edition*, December 2001, page 43. A copy of the article is attached.) In many cases, the triptans can be used to *completely abort* a migraine headache. Triptans are indicated for use in migraine headaches, but not for headaches resulting from blunt force trauma, dehydration, and sinus congestion. (Imitrex Prescribing Information, pages 6-7.)

It is unreasonable to suggest that a practitioner would fail to consider, or ignore, the underlying causes of a headache in choosing a treatment. Some headaches are merely symptoms of a serious underlying disease requiring treatment. Other headaches, such as migraines, are the primary manifestation of the disease itself but respond poorly to common analgesics such as acetaminophen and ibuprofen. In such cases, the best treatment may be directed at the underlying cause of the pain, not at the pain itself.

The Office's suggestion that voiding dysfunction is like headaches, in that one would treat the symptom with a particular drug regardless of the cause, is in error. Voiding dysfunction is a secondary symptom associated with various diseases, and is classified into (1) neurogenic bladder caused by cerebrospinal disease, cerebrovascular accident, diabetes mellitus, peripheral nervous disturbance, etc., (2) organic lower urinary tract obstruction such as benign prostatic hypertrophy (BPH) and urethral stricture, and (3) contraction insufficiency of bladder caused by stress urinary incontinence in adult females, prostatitis, prostatic cancer, and anticholinergic agents.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

(Specification, paragraph bridging pages 1 and 2.) Thus, there are various underlying causes of voiding dysfunction.

The Office cites Yasuda et al. for the disclosure that alpha blockers are useful in treating voiding dysfunction associated with BPH. Applicant notes that the voiding dysfunction associated with BPH is caused by urethral stricture from compression of enlarged prostate and by over-shrinkage of prostate smooth muscle, combined with an increase in α_1 receptors in the enlarged prostate and in the urethral tissue. (Specification, page 2, first full paragraph; Kondo et al., *British Journal of Urology* 72, 68-73 (1993).) Tamsulosin lowers intraurethral pressure in voiding dysfunction associated with BPH, at least in part, by blocking the α_1 receptor in the prostate tissue of affected males. (Chapple et al., *Eur. Urol.* 32: 462-470, 463, first full paragraph.) In urinary dysfunction resulting from BPH, the overconstriction of the *prostate tissue* and *urethra* are major components causing the functional obstruction of the urethra. (Id., page 463, first column, lines 2-6; Kondo et al.) Thus, by blocking this overconstriction in the prostate, tamsulosin effectively reduces intraurethral pressure. One of skill in the art would not expect tamsulosin to be effective in men without enlarged prostates, or in women, who entirely lack a prostate.

The Office's arguments make clear that it believes the *reason* for choosing a particular treatment is irrelevant and that the underlying primary disease has no impact on the choice. Applicant's claims, however, explicitly recite the underlying primary disease, i.e., "neurogenic bladder," and it is not appropriate for the Office to ignore that recitation. (See *Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 34 USPQ2d 1565 (Fed.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Cir. 1995)). Applicant submits that when this recitation is considered as an element of the claim, the rejection for obviousness should be withdrawn.

In view of the foregoing amendment and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of the pending claim.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: April 9, 2003

By: Sean Myers-Payne

Sean Myers-Payne
Reg. No. 42,920
ph. (571) 203-2717
fax (202) 408-4400
sean.myers-payne@finnegan.com

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

APPENDIX TO AMENDMENT

The application is amended as follows:

IN THE CLAIMS:

Claim 4 is amended as follows:

4. (ONCE AMENDED) A method [for the therapy of] of treating voiding dysfunction associated with neurogenic bladder, [where said method includes administration of] comprising administering tamsulosin or a pharmaceutically acceptable salt to a patient, wherein the patient does not exhibit lower urinary tract obstruction.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com